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Does response inhibition have pre- and post-diagnostic utility in Parkinson's disease?

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Abstract

Parkinson's disease (Pd) is the second most prevalent degenerative neurological condition worldwide. Improving and sustaining quality of life is an important goal for Parkinson's patients. Key areas of focus to achieve this goal include earlier diagnosis and individualized treatment. This review discusses impulse control in Pd and examines how measures of impulse control from a response inhibition task may provide clinically useful information i) within an objective test battery to aid earlier diagnosis of Pd and ii) in post diagnostic Pd, to better identify individuals at risk of developing impulse control disorders with dopaminergic medication.

1. Introduction

Parkinson's disease (Pd) is a relatively common progressive neurodegenerative disease affecting about 6.3 million people worldwide (Apaydin, Ahlskog, Parisi, Boeve, & Dickson, 2002; Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; EPDA, 2014). The pathological process which underlies Pd relentlessly progresses to the full-blown clinical syndrome over several years (Braak et al., 2004). Pd is associated with the degeneration of dopaminergic nigrostriatal neurons in the substantia nigra pars compacta (SNpc) (Apaydin et al., 2002; Cameron, Watanabe, Pari, & Munoz, 2010; Gradinaru, Mogri, Thompson, Henderson, & Deisseroth, 2009), as well as several other nuclei of the brainstem (Grinberg, Rueb, Alho, & Heinsen, 2010). Although motor symptoms are common landmarks for diagnosis and staging, Pd also involves disturbances in cognitive, limbic and autonomic systems.

Currently there is no definitive test for Pd, making diagnosis relatively subjective. Clinical presentation of the disease can fluctuate over time, complicating disease monitoring and treatment evaluation. In addition, the pathology of this disease is only diagnostic in the brainstem which is difficult to study during life, adding to the challenge of unbiased and objective monitoring. The time between the onset of neurodegeneration and the ability to clinically diagnose Pd is termed the pre-diagnostic phase (Gaenslen, Swid, Liepelt-Scarfone, Godau, & Berg, 2011; Truong & Wolters, 2009). During the pre-diagnostic phase, irretrievable dopaminergic neuron loss in the SNpc has not yet reached the threshold for diagnosis. This phase presents an opportunity for treatment optimization through earlier diagnosis using tools that are sensitive enough to identify early changes in biological systems. The aim of earlier diagnosis

would be to enable early neuroprotective therapies to prevent or delay further neuron degeneration (Berg & Poewe, 2012).

Once diagnosed, there are further challenges presented to patients and clinicians from treatment side effects. The two most common forms of treatment are medication and surgery (deep brain stimulation, pallidotomy, etc.). One prevalent, under-reported and detrimental side effect to dopaminergic medication treatment is the development of impulse control disorders, which manifest as impulsive and compulsive behaviours in a variety of contexts. Treatment decisions would be aided by an objective method to predict and classify an individual's risk of impulsivity with dopaminergic treatment.

This review focuses on impulse control in Pd and how objective measures of impulse control could be used clinically pre and post diagnosis. The review has three main aims. First, to review and summarise functional changes in frontostriatal and basal ganglia-thalamocortical networks in Pd and their effect on impulse control, specifically response inhibition. Secondly, to introduce the potential of standardised response inhibition paradigms from motor behaviour research to provide useful measures within an objective test battery to identify insidious motor and non-motor changes during the pre-diagnostic phase, and aid earlier diagnosis. Third and finally, we introduce the idea of combining information obtained from response inhibition tasks with genetic analysis in the post-diagnostic phase of Pd to better identify mechanisms which predispose individuals to impulse control disorders with dopaminergic treatment.

2. Impulse control in Pd

Execution of premature or inappropriate responses reflects poor impulse control (Duque & Ivry, 2009). There are two aspects of impulse control: cognitive/psychological and motor/behavioural (Nemoda, Szekely, & Sasvari-Szekely, 2011). Impulsive decision making (i.e. dysfunctional cognitive impulse control) manifests as an inability to evaluate the potential consequences of a decision and modify the decision accordingly, and has been associated with inferior structural integrity of white matter projections between the PFC and striatum (Peper et al., 2013). The inability to suppress an unnecessary action (i.e. impaired response inhibition) is an example of the motor/behavioural aspect (Nemoda et al., 2011).

There is a general decrease in impulse control with aging, seen in motor (Braver & Barch, 2002; Fisk & Sharp, 2004), and cognitive impulse control (Fisk & Sharp, 2004). The age-related deterioration of motor impulse control is exacerbated with BG dysfunction as is evident in focal dystonia (Stinear & Byblow, 2004) and Pd (Bokura, Yamaguchi, & Kobayashi, 2005; Cooper, Sagar, Tidswell, & Jordan, 1994; Gauggel, Rieger, & Feghoff, 2004; I. Obeso et al., 2011). A dose-dependent inverted-U relationship (Goldman-Rakic, Muly Iii, & Williams, 2000) has been hypothesized to explain observed behavioural changes in impulse control associated with changes in dopamine neurotransmission in the prefrontal cortex (PFC) (Robbins & Arnsten, 2009). For those with lower levels of dopamine neurotransmission, increasing PFC dopamine concentration promotes better motor (Congdon, Constable, Lesch, & Canli, 2009) and cognitive impulse control (Diamond, Briand, Fossella, & Gehlbach, 2004)and decreased impulsivity (Farrell, Tunbridge, Braeutigam, & Harrison, 2012).

2.1 Evidence for motor tests as biomarkers for Pd

Deterioration of the motor system occurs well in advance of the clinical diagnosis of Pd. Evidence of subtle motor deficits exists during the pre-diagnostic stage. Therefore salient tests of motor function could become possible biomarkers. Years before clinical diagnosis patients subjectively report increased stiffness, slowness of movement, changes in gait pattern, reduced arm swing, tremor, and postural imbalance (de Lau, Koudstaal, Hofman, & Breteler, 2006; Gaenslen et al., 2011). Movement tasks are capable of providing objective measures of these abnormalities. Tasks of visuomotor control (Hocherman & Giladi, 1998) and handwriting (Horstink & Morrish, 1999) have identified deficits in the asymptomatic hand of patients in the early stage of Pd. Movement tasks which are able to detect subtle deterioration of motor control show greatest potential as biomarkers.

Motor deficits are present in *de novo* Pd patients compared to healthy age-matched controls. For example, *de novo* Pd patients show impaired upper limb performance during bimanual (Ponsen et al., 2006) and unimanual (Pfann, Buchman, Comella, & Corcos, 2001; Ponsen, Daffertshofer, Wolters, Beek, & Berendse, 2008) movements. During a complex bimanual circle-drawing task, measures of success rate and accuracy are lower in Pd patients, especially in the non-dominant hand (Ponsen et al., 2006). However, even simple unimanual movement tasks reveal impairments in modulation of muscle activity and coordination in *de novo* patients (Pfann et al., 2001; Ponsen et al., 2008). Pfann and colleagues demonstrated that EMG can reveal an inability to modify movements according to task demands (impaired motor set) in *de novo* Pd patients during a rapid elbow flexion task. EMG traces of patients reveal an impaired modulation of muscle bursting during upper limb movements of both single-joint (Hallett & Khoshbin, 1980; Vaillancourt, Prodoehl, Verhagen Metman, Bakay, & Corcos, 2004)

and multi-joint movements (Farley, Sherman, & Koshland, 2004). EMG activity patterns are therefore a potentially sensitive motor measure for identification of Pd, with one study finding 90% sensitivity at differentiating individuals with Pd from healthy controls during single-joint point-to-point flexion movements (Robichaud et al., 2009). Of note, one healthy control who demonstrated abnormal EMG was subsequently diagnosed with Pd 30 months later. Ultimately, evidence exists that non-invasive and objective motor measures from EMG have the potential to reveal subclinical neurophysiological abnormalities during the pre-diagnostic stage.

2.2 Response inhibition in Pd

2.2.1 Functional changes in basal ganglia-thalamocortical networks with Pd

Nuclei of the BG are an integral part of the sensorimotor system, forming a cortico-subcortico-cortical loop involved in planning, executing and cancelling responses. Response inhibition (RI) depends critically upon interactions between the right frontal cortex (in particular, the right inferior frontal gyrus) and the BG (Aron, Durston, et al., 2007; Aron & Poldrack, 2006; Coxon, Van Impe, Wenderoth, & Swinnen, 2012; Jahfari et al., 2011; Robbins, 2007; Swann et al., 2011; Zandbelt & Vink, 2010). Striatal grey matter atrophy has been linked to impaired RI in Pd (O'Callaghan, Naismith, Hodges, Lewis, & Hornberger, 2013). The striatum is the main input to the BG, receiving projections from the cerebral cortex, midbrain and thalamus (Figure 1). The striatum is divided into dorsal (caudate nucleus and putamen, separated by the internal capsule) and ventral regions (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013). BG sensorimotor networks comprise the motor portions of the putamen, i.e. dorsal striatum (Alexander & Crutcher, 1990; Kandel et al., 2013).

Projecting from the dorsal striatum are two parallel pathways through the BG: the 'direct' and 'indirect' pathways (Figure 1). Both pathways modulate thalamic output to the cortex by either increasing ('direct') or decreasing ('indirect') thalamocortical drive (Alexander & Crutcher, 1990; Danion & Latash, 2011). The STN has been recognized as another significant input structure of the BG (Coizet et al., 2009; Lanciego et al., 2004). A third 'hyperdirect' pathway projecting from the cortex can rapidly decrease thalamocortical drive (i.e. an inhibitory pathway) without synapsing onto the striatum, but rather directly onto the STN (Nambu, Tokuno, & Takada, 2002). Figure 1 illustrates examples of hyperdirect pathways from the inferior frontal cortex and the pre-SMA connecting directly to the STN. Evidence suggests that 'hyperdirect' pathways are critical for successful response inhibition (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Coxon et al., 2012; King et al., 2012).

The main BG output nuceli are internal globus pallidus (GPi) and substantia nigra pars reticulata (SNpr). These two structures provide sustained inhibitory input onto thalamocortical neurons. The general consensus is that movement initiation (through facilitation of the 'direct' pathway) is an active process, requiring a pause in tonic inhibition and disinhibition of the thalamus. The default state of the motor system is analogous to driving with the brakes on, or the 'hold your horses' model (Ballanger et al., 2009). The spatial and temporal recruitment of the 'direct', 'indirect' and 'hyperdirect' pathways gives rise to the complex functionality of the BG.

The balance of neuronal output from the three BG pathways is usually maintained by dopamine through dopaminergic projections from the SNpc to all BG nuclei, but most significantly through the dense connections to the dorsal and ventral striatum (Bjorklund & Dunnett, 2007). The origins of the 'direct' and 'indirect' pathways are from separate populations of striatal medium spiny neurons. The 'direct' pathway originates from neurons expressing

predominantly D1 dopamine receptors (DRD1), and the 'indirect' pathway from neurons expressing predominantly D2 receptors (DRD2). Dopaminergic projections from the SNpc differentially activate the two striatal neuronal populations due to the different dominant postsynaptic receptors. Dopamine binding to DRD1 facilitates the 'direct' pathway, whereas dopamine binding at DRD2 suppresses the 'indirect' pathway (Danion & Latash, 2011; Gerfen et al., 1990; Kandel et al., 2013; J. A. Obeso, Guridi, Nambu, & Crossman, 2013). The presence of dopamine therefore modulates movement control by reinforcing any cortically initiated activation of BG-thalamocortical networks leading to disinhibition of thalamocortical neurons (Alexander & Crutcher, 1990).

In Pd, RI is disrupted by dopamine disturbance within the sensorimotor BG-thalamocortical network. The degeneration of nigrostriatal dopaminergic neurons reduces the dopaminergic modulation through reduced striatal dopamine levels (Kandel et al., 2013). Reduced striatal dopamine results in less activation of striatal DRD1 and DRD2 affecting the 'direct' and 'indirect' pathways, respectively. Through decreased activation of DRD2s, striatal inhibitory projections to the GPe become more active through reduced suppression. There is increased striatal inhibition of the GPe, subsequent disinhibition of the STN and therefore STN hyperactivity within the 'indirect' pathway. Simultaneously, striatal projections to the GPi and SNpr become less active through decreased DRD1 activation (Alexander & Crutcher, 1990). As a result of increased STN excitation and reduced striatal inhibition, there is increased activity of the GPi and SNpr, and a subsequent increase in tonic inhibition of the thalamocortical projection neurons. Therefore, with Pd, maladaptive modulation of tonic inhibition of the thalamus through the separate striatal neuron subpopulations and subsequent BG pathways (Albin, Young, & Penney, 1989) has a crucial impact on motor impulse control i.e. response inhibition.

2.2.2 Functional changes in frontostriatal networks with Pd

In Pd, abnormal modulation of striatal and PFC dopamine results in dysfunction within frontostriatal networks (Shepherd, 2013) and impaired impulse control. Networks involving the PFC and striatum are implicated not only in motor control, but also in several cognitive functions, including memory, action selection, behaviour reinforcement, and contextual conditioning (Alexander & Crutcher, 1990; Goto & Grace, 2005; Pennartz et al., 2009). Dysfunction of frontostriatal networks can therefore contribute to a multitude of symptoms. As with many biological systems the key to optimizing function is balance. The optimal range for dopaminergic neurotransmission for frontostriatal networks is best illustrated by the inverted-U relationship. For example, the optimal range of PFC dopaminergic neurotransmission is surrounded by that above or below optimal (Figure 2), resulting in decreased PFC function. However the relationship between dopamine and functional performance is also complex, and includes several contributing factors.

Reducing dopamine neurotransmission can impair certain functions while enhancing others. The functional state of the PFC relates to RI performance. RI tasks are sensitive to cognitive deficits as well as motor impairments, and are essentially cognitive-motor tasks. In addition to proficient motor impulse control, RI also requires efficient attention control (Tachibana, Aragane, Miyata, & Sugita, 1997) and cognitive flexibility (Cooper et al., 1994), both of which recruit the PFC. Decreasing prefrontal dopamine promotes cognitive flexibility in young (Blasi et al., 2005; Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010) and older (Fallon, Williams-Gray, Barker, Owen, & Hampshire, 2013) healthy individuals and Pd

patients (Cools, Miyakawa, Sheridan, & D'Esposito, 2010), at the expense of cognitive stability. These findings are in line with Dual State Theory (Durstewitz & Seamans, 2008) whereby a DRD1 dominated system contains high energy barriers between neural state representations. This system therefore favours stability and perseveration. Conversely, a DRD2 dominated system favours switching between representational states through low energy barriers. Direct neurophysiological evidence for Dual State Theory is supported by rodent models (Goto & Grace, 2005). The inverted-U relationship explains why equivalent changes to dopaminergic neurotransmission can have opposite effects on cognitive functions.

In early Pd, dopamine concentrations are decreased within regions of the SN and striatum, yet paradoxically dopamine concentration is increased in the PFC (Kaasinen et al., 2001). This counterintuitive increase in PFC dopamine could reflect compensation within the mesocorticolimbic (MCL) network (Rakshi et al., 1999; Zigmond, Abercrombie, Berger, Grace, & Stricker, 1990). It could be due to reduced striatal dopamine levels, given the well-studied inverse relationship between MCL and nigrostriatal dopaminergic systems (Akil et al., 2003; Carr & Sesack, 2000; Carter & Pycock, 1980; Jahanshahi et al., 2010; Kolachana, Saunders, & Weinberger, 1995; Pycock, Carter, & Kerwin, 1980; Roberts et al., 1994; Sawamoto et al., 2008). A hyperdopaminergic MCL network causes greater dopamine transmission between the ventral tegmental area and PFC. In the early stages of Pd, the increase in PFC dopamine effectively ‘shifts’ patients to the right of the curve compared to healthy controls. Crucially, a shift to the right may increase or decrease cognitive performance by moving the individual into or beyond the optimal range of dopamine for a task. Average young healthy individuals cluster toward the left of the inverted-U while early Pd patients tend to cluster toward the right (Figure 2). Higher prefrontal dopamine enhances attentional control (required for RI) in healthy

individuals (Blasi et al., 2005) but impairs it in patients (Williams-Gray, Hampshire, Barker, & Owen, 2008). These findings illustrate how increasing dopamine in early Pd has opposite effects on prefrontal function and neural activity compared to younger healthy individuals (Fallon et al., 2013).

Measures of RI demonstrate strong potential to objectively identify abnormalities in the frontostriatal and sensorimotor BG-thalamocortical networks inherent to Pd. Midbrain and cortical regions such as the striatum, SN, STN, globus pallidus, supplementary motor area/pre-supplementary motor area and PFC, all demonstrate impaired activity in Pd as described above. These areas form part of the right-lateralized inhibitory control network which projects input to the primary motor cortex via the thalamus (Figure 1) (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron & Poldrack, 2006; Bellgrove, Hester, & Garavan, 2004; Coxon, Stinear, & Byblow, 2006, 2009; Garavan, Ross, & Stein, 1999; Liddle, Kiehl, & Smith, 2001; Mostofsky et al., 2003; Picard & Strick, 1996; Rubia, Smith, Brammer, & Taylor, 2003; Stinear, Coxon, & Byblow, 2009). Furthermore, involvement of the PFC could mean RI tasks are sensitive to prefrontal cognitive deficits present in the disease. Here we examine only RI tasks that require observable motor behaviour, as opposed to other types of behavioural inhibition, such as the Stroop Colour Word test or tests of deferred gratification.

3. Response inhibition tasks in pre-diagnostic Pd

Motor RI has traditionally been investigated using a stop-signal or go/no-go task. These tasks involve externally cued motor responses. An anticipatory response inhibition (ARI) task (Slater-Hammel, 1960) allows investigation of internally cued anticipated motor responses. All three RI tasks have provided useful insights into the initiation and inhibition processes required for successful control of a motor response. The primary dependent measures for each task and

the expected affect of Pd on each measure is presented in Table 1. Subtle design differences between the tasks enables the examination of cancelling three fundamentally different processes; a planned, externally generated or internally generated action. There is therefore the question as to which task design is optimally suited to identify Pd biomarkers. To date there are published studies using go/no-go and stop-signal paradigms in Pd, but no published studies using an ARI task with Pd patients.

3.1 Go/no-go task

The majority of trials in the motor go/no-go task require participants to make a motor response as quickly as possible when a Go cue is presented. Occasionally the Go signal is replaced by a No-Go signal (Figure 3A), indicating the participant should make no response. The go/no-go task design examines the ability to withhold a planned response (i.e. action restraint) which is often necessary to resolve pre-response conflict. The go/no-go task has been used to examine RI in Pd. Individuals with Pd have delayed reaction times (RTs) (Cooper et al., 1994; Tachibana et al., 1997) and greater error rates (Bokura et al., 2005) compared to healthy controls on this task, supporting ideas of impaired conflict resolution in Pd (Cooper et al., 1994). However, unlike the earlier studies, Bokura et al. found no significant difference in RTs between Pd patients and controls. Yet the decreased accuracy of patients, specifically the higher rate of false alarm responses, may indicate the presence of a speed-accuracy trade-off; RTs shortened at the expense of accuracy. More recent studies conflict with the results of earlier studies. For example, no difference in error rate or RT between Pd patients and healthy controls (Beste, Willemssen, Saft, & Falkenstein, 2010). Furthermore, RTs and error rates on the go/no-go task were unable to distinguish between healthy controls and patients with early Pd (Baglio et al., 2011). RT could not differentiate between *de novo*, early treated and chronic Pd patients (Cooper

et al., 1994). Overall the contradictory findings suggest the go/no-go task lacks sufficient sensitivity in the context of Pd. The lack of sensitivity and correlation to disease severity suggests measures from this type of RI task are inappropriate biomarkers for Pd.

3.2 Stop-signal task

The stop-signal task has played an integral part in elucidating the role of BG and cortical structures which form the right-lateralized inhibitory control network. The majority of trials again require a motor response as quickly as possible to an external Go signal. On some trials, a Stop signal is presented at a variable delay *after* the Go signal (stop-signal delay, SSD) (Figure 3B, left). Longer SSDs increase the probability of an incorrect response. The SSD can change dynamically during the task using a staircase procedure to ensure convergence to a stop time that results in 50 % probability of successful inhibition: $p(\text{respond}) = 0.5$. The task design enables the measurement of the efficacy and the latency of the inhibitory process, calculated as the difference between the Stop signal for $p(\text{respond}) = 0.5$ and mean RT on Go trials (stop-signal reaction time, SSRT) (Figure 3B, right). Interpretation of the SSRT is based on the 'horse-race' model (De Jong, Coles, Logan, & Gratton, 1990; Logan & Cowan, 1984), built on the premise of independent excitatory and inhibitory mechanisms. Response execution is a result of excitatory mechanisms, triggered by the Go signal. Inhibitory mechanisms are triggered by the Stop signal, which prevent response execution. Whichever mechanism 'wins the race' determines whether a motor response is generated. The SSRT signifies the latency at which each mechanism 'wins' half the time. SSRT is often used to examine the integrity of inhibitory mechanisms.

The stop-signal task has been used to examine motor control in Pd. Mild to moderately advanced Pd patients have difficulty initiating and inhibiting responses during the stop-signal task (Gauggel et al., 2004; Mirabella et al., 2012; I. Obeso et al., 2011; Swann et al., 2011)

compared to controls, manifesting as slower RTs and longer SSRTs. RI motor deficits are accompanied by deficits in volitional inhibition on cognitive tests (I. Obeso et al., 2011), supporting the presence of generalized impulse control deficits in Pd. Curiously, Gauggel and colleagues (2004) were unable to find a correlation between impaired RI and disease severity in Pd.

To be sensitive to the progressive degeneration associated with disease severity, a task needs to adequately recruit and challenge the BG system. Although the stop-signal and go/no-go tasks offer advantages from having well-defined go and stop cues, they require participants to respond to external cues (i.e. a signalled response). Externally cued movements require less involvement of the BG system compared to internally generated movements (Jahanshahi et al., 1995). Therefore, measures taken during inhibition of externally generated movements are less likely to be sensitive to the ongoing deterioration of the BG network integrity during Pd. Additionally, probability of successful inhibition on the stop-signal task increases with slower RTs to the go signal (Lappin & Eriksen, 1966). Lappin and Eriksen (1996) were the first to observe that participants could delay their response to improve their chance of successful inhibition if a stop cue was presented. More recently, it has again been acknowledged that the stop-signal task allows adjustments to response strategies (e.g. slowing of responses) to balance the requirements of execution and inhibition (Verbruggen & Logan, 2009). The stop-signal task may therefore be better described as investigating action postponement. If patients are aware of their deteriorating impulse control, they may adjust their response strategy and slow down, or postpone, their response to enable better reaction to the stop cue. The delayed patient RTs reported by Gauggel et al. (2004) may be reflecting such a strategy.

3.3 Anticipatory response inhibition tasks

The ARI paradigm is based on that of Slater-Hammel (1960). In the original study, healthy young participants anticipated and stopped the sweep dial of a clock face at a target position by depressing a switch. Subsequent studies have used a rising or 'filling' bar (Coxon, Stinear, & Byblow, 2007; MacDonald, Stinear, & Byblow, 2012; Yamanaka & Nozaki, 2013; Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2013; Zandbelt & Vink, 2010). The stop signal consists of the indicator automatically stopping *before* the target (Figure 3C, left). Slater-Hammel found that participants had a 50 % probability of successfully inhibiting their prepared response when the sweep dial stopped 166 ms before the target. With ARI the closer in time that the Stop signal is to the target position, the greater the probability that a Go response will be generated. As with the stop-signal task, the timing of the Stop signal can be programmed to converge on a stop time that produces 50 % successful inhibition to allow the calculation of SSRT. Thus, ARI tasks also permit the estimation of latency and accuracy of inhibition (Figure 3C, right). In ARI, response execution is relatively constrained compared to other RI tasks, as response times are tightly distributed around a defined target. This is because ARI tasks require participants to internally generate and inhibit an anticipated motor response rather than react to a signal. The anticipatory nature of the default response enables the examination of volitional inhibition during preparation of an internally generated response.

ARI tasks produce interesting results with individuals with BG disorders. For example patients with focal hand dystonia (FHD) have an increased latency and decreased efficacy of their motor inhibitory process (Stinear & Byblow, 2004). In this study, the indicator had to stop a greater distance from the target position for patients than healthy controls, to obtain a 50 % probability of successful inhibition (lower R50, Figure 4A). When patients did successfully

inhibit their response, they demonstrated a greater probability of partial EMG bursts in the agonist muscle even with no overt movement (Figure 4B), indicating the production of an incomplete response. Overall, ARI measures and EMG revealed that FHD patients had greater difficulty inhibiting their anticipated motor response compared to healthy age-matched controls.

Although much is known about deficits in simple and choice reaction times in Pd based on externally cued tasks, less is known about the self-initiation and cancellation of anticipatory responses. An ARI task has not yet been used in a published study with Pd patients. Nevertheless, preliminary data with *de novo* patients and healthy age-matched controls indicate novel insights into elements of voluntary control using an ARI task (unpublished data). Apart from decreased accuracy on execution trials, *de novo* patients also show abnormal EMG patterns of activation prior to initiation of the motor response (Figure 4C, D). Patients demonstrate a predominance of multiple, ineffective EMG bursts during execution trials, contributing to indications that EMG activity patterns may be a sensitive motor measure for identification of Pd (Farley et al., 2004; Hallett & Khoshbin, 1980; Pfann et al., 2001; Vaillancourt et al., 2004). Taken together, the variability in response times and abnormal EMG patterns signify patients have difficulty suppressing their imminent response and timing it correctly to intercept the target, indicating deficits in predictive internal motor timing. Temporal processing and movement timing, required for successful predictive internal motor timing, recruit the PFC (Jahanshahi et al., 2010) and dopaminergic BG pathways (Meck, 1996; O'Boyle, Freeman, & Cody, 1996), specifically the SN (Fan, Rossi, & Yin, 2012). So it logically follows that Pd patients would experience internal motor timing deficits (Harrington, Haaland, & Hermanowicz, 1998; Malapani et al., 1998; Pastor, Jahanshahi, Artieda, & Obeso, 1992), as indicated by the response times and EMG patterns from the pilot data. Nevertheless, this is not always the case (Bareš,

Lungu, Husárová, & Gescheidt, 2010). On the other hand, Bares and colleagues only reported behavioural results. The novel motor control deficits revealed by the pilot study were not evident at a purely behavioural level. EMG recordings were used in combination with the task to reveal the abnormalities. An ARI task, in combination with EMG, may be able to reveal abnormalities of motor function beyond current clinical examination abilities.

Interestingly, the preliminary results with the ARI task were able to distinguish between *de novo* patients and controls on Go trials, with the EMG and behavioural data revealing deficits in internal motor timing. Given these results, and the fact that SSRT does not always correlate with disease severity (Gauggel et al., 2004), Go trials in the context of a RI task might provide the more sensitive and useful biomarkers during the pre-diagnostic period.

Overall, the ARI task satisfies the three criteria necessary to obtain quantitative, objective and sensitive measures of the motor deficits during the pre-diagnostic phase of Pd (Maetzler & Hausdorff, 2012): 1) ARI challenges the BG system by requiring generation and cancellation of internally-generated movements, 2) used in combination with EMG measures, ARI can be used to assess motor function beyond clinical evaluation standards and 3) ARI can distinguish between patients and controls at the earliest phase of the disease. Given these three main criteria, ARI may also be able to monitor Pd progression, although further research will be required to test this.

The positive results produced using the go/no-go and stop-signal tasks in the context of Pd serve to motivate the use of RI tasks with Pd patients in the pre-diagnostic stage. Theoretically, for reasons stated above, an ARI task may perform even better at differentiating between healthy controls and pre-diagnostic Pd patients. This theory is supported by the pilot data using an ARI

task with *de novo* patients. However more research is certainly needed and it is currently unclear which RI task would reveal the most salient biomarkers of Pd.

3.4 Bimanual response inhibition

The majority of RI studies have investigated execution and cancellation of simple unimanual responses, with or without a preceding choice decision. Fewer studies have investigated execution and cancellation of unitary, bimanual responses using either the stop-signal (Aron & Verbruggen, 2008; Claffey, Sheldon, Stinear, Verbruggen, & Aron, 2010; Ko & Miller, 2011; Majid, Cai, George, Verbruggen, & Aron, 2012) or ARI task (Coxon et al., 2007, 2009; Coxon et al., 2012; MacDonald et al., 2012). There is evidence to suggest that bimanual RI tasks may be even more salient than unimanual RI in the context of Pd. Individuals with Pd demonstrate impaired bimanual coordination, especially in an anti-phase pattern (Almeida, Wishart, & Lee, 2002; Byblow, Summers, Lewis, & Thomas, 2002; Geuze, 2001; Ponsen et al., 2006) or when performing two different movements simultaneously (Brown, Jahanshahi, & Marsden, 1993). Importantly, bimanual coordination dysfunction is present in *de novo* Pd (Ponsen et al., 2006). In-phase movements require symmetric activation of homologous muscles, whereas anti-phase movements require simultaneous activation of non-homologous muscles. MacDonald et al. (2012) investigated bimanual ARI performance and compared homologous versus non-homologous muscles. Surprisingly, healthy younger adults are able to perform the task equally well with both muscle pairings. However Pd patients would be expected to exhibit worse performance using non-homologous muscle pairings. Importantly, since the ARI task effectively constrains the Go response, it should provide a valid estimate of the inhibitory process in Pd patients. A bimanual RI task may reveal more subtle motor deficits than unimanual RI for pre-diagnostic Pd.

Another advantage of a bimanual task is that it permits the examination of partial response cancellation, a cognitively and neurophysiologically demanding behaviour. When a subset of an action must be cancelled while the remaining components continue, the remaining components are substantially delayed (Aron & Verbruggen, 2008; Claffey et al., 2010; Coxon et al., 2007, 2009; Ko & Miller, 2011; MacDonald et al., 2012). Furthermore the subsequently delayed response is executed at a higher gain as indicated by a greater rate of EMG onset and force production (Coxon et al., 2007; Ko & Miller, 2011; MacDonald et al., 2012). The delay and gain of EMG is greater with homogeneous digit pairings compared to heterogeneous pairings (MacDonald et al., 2012). Given the expected damage to gain setting nuclei in the brainstem that accompanies early Pd (Braak et al., 2004; Grinberg et al., 2010), the bimanual ARI paradigm of MacDonald et al. (2012) may be salient for detecting the onset of Pd.

4. Pre-diagnostic Pd: RI tasks as a component of an objective test battery

We propose that RI tasks have potential utility during the pre-diagnostic stage to reveal subtle, sub-clinical motor abnormalities to aid with earlier diagnosis of Pd. The diagnosis of Pd currently remains a clinical one, with no definitive biochemical or genetic diagnostics. The only definitive Pd diagnosis is through a post-mortem. Diagnosis is particularly difficult in the very early stages of the disease, and is based on the presentation of motor symptoms and a positive response to Pd medication. Unfortunately, there is a substantial length of time between the onset of neurodegeneration and the ability to clinically diagnose Pd. This period is known as the pre-diagnostic (prodromal) phase, also referred to as the pre-motor phase, and can last up to ten years (Gaenslen et al., 2011; Gonera, van't Hof, Berger, van Weel, & Horstink, 1997). However our

contention is that pre-motor is not an appropriate term given the evidence of motor abnormalities during this time. For simplicity we refer to this stage as pre-diagnostic.

Biomarkers are objectively measurable characteristics indicative of normal biological processes (Michell, Lewis, Foltynie, & Barker, 2004). One of the most basic goals for biomarkers is to help shorten the pre-diagnostic stage of Pd, and to facilitate better treatment and ultimately better quality of life. It is estimated that 50 – 70 % of irretrievable dopaminergic neuron loss is needed in the SNpc to develop the characteristic symptoms required for clinical diagnosis (Fearnley & Lees, 1991; Marino et al., 2012; Riederer & Wuketich, 1976). This means the extent of degeneration has not yet reached this critical point during the majority of the pre-diagnostic phase, providing a window of opportunity for early neuroprotective therapies to prevent or delay further neuron degeneration. The goal of earlier diagnosis is therefore an important one. For example, if it were possible to diagnose Pd early in the pre-diagnostic stage and a causal therapy was available, then further neuronal loss in the SNpc may even be preventable (Braak et al., 2003).

During the pre-diagnostic phase unspecific symptoms appear in isolation. For this reason, such symptoms are only confirmed retrospectively after clinical diagnosis, but it is also possible for healthy individuals to exhibit many of these unspecific symptoms as part of normal ageing e.g. impaired sense of smell, disturbed sleep, balance disturbance, muscle stiffness. Although the simple occurrence of select symptoms is not sufficient for a Pd diagnosis (Gaenslen et al., 2011), the presentation of certain symptoms in a predicted chronological order (Braak et al., 2003; Przuntek, Muller, & Riederer, 2004) may identify a higher risk for Pd. It has been proposed that at least two positive tests on potential pre-diagnostic symptoms may be considered sufficient evidence to diagnose a patient as clinically possible to have Pd and begin protective therapy

(Truong & Wolters, 2009). Affirmation of this probable diagnosis may be acquired through a response to Pd treatment.

For a measure to be useful for early detection in Pd, it is necessary to prospectively investigate a group of individuals at risk of developing the disease. However, the first step is to examine whether the measure is capable of discriminating between a diagnosed group at the earliest stage of the disease and healthy age-matched controls. Before a test is deemed to have clinical utility, research is required to verify its sensitivity, specificity and plausibility. If one can assume that severity distinguishes between the pre-diagnostic and early clinical (*de novo*) state, it can be inferred that tests which are successful at differentiating between *de novo* patients and controls also show promise for differentiating during the pre-diagnostic stage.

Several techniques are currently under investigation for identifying early and subtle non-motor changes to biological processes during the pre-diagnostic stage (for a review see Michell et al. 2004). These include MRI (Gattellaro et al., 2009; Lewis, Dove, Robbins, Barker, & Owen, 2003; Martin, Wieler, & Gee, 2008; Peran et al., 2010; Tessa et al., 2008), transcranial sonography (Izawa, Miwa, Kajimoto, & Kondo, 2012), cerebral spinal fluid analyses (Goldstein, Holmes, & Sharabi, 2012), rapid eye movement (REM) sleep disturbance, olfactory function, protein build-up in colonic neurons (Shannon, Keshavarzian, Dodiya, Jakate, & Kordower, 2012), amongst others. A full discussion of non-motor biomarkers is beyond the scope of this review. However it is worth noting that the most prevalent non-motor symptoms of Pd involve specific brainstem nuclei (for a review see Grinberg et al. 2010). For example, neurodegeneration in the olfactory bulb leads to olfactory dysfunction and lesions within the medulla oblongata and pontine tegmentum are involved in REM sleep behavioural disorder (Braak et al., 2003; Braak et al., 2004; Del Tredici, Rüb, De Vos, Bohl, & Braak, 2002). Due to

the neurobiological pattern of Pd progression, olfactory and REM sleep behaviour disorder symptoms appear before degeneration of SNpc neurons which cause motor symptoms. For this reason, we regard these non-motor biomarkers as optimal for combined use with a RI task into an objective test battery, to utilize the crucial period when damage to dopaminergic neurons may be preventable, or at least delayed. Biomarkers derived from magnetic resonance imaging (MRI) may also complement the early behavioural manifestations of Pd and prove useful in objectively monitoring disease progression. It is unlikely that any single biomarker will be perfect for Pd. Due to the heterogeneity of the disease, it is more likely that a faction of biomarkers will be required.

5. Post-diagnostic Pd

5.1 Response inhibition and impulse control disorders

Response inhibition tasks may also have utility in post-diagnostic Pd and for evaluating treatment options. One prevalent, detrimental and under-reported side effect of dopaminergic medication in Pd is the prevalence of impulse control disorders (ICDs). The incidence of ICDs in Pd patients is as high as 20% (Weintraub, 2009), and suggests some individuals have greater susceptibility for developing ICDs than others. The identified risk factors for ICDs include age at Pd onset with ICD more prevalent in younger patients, being male, being single, having a family or personal history of addictive behaviours, dopamine agonist medication in combination with levodopa treatment, high doses of dopaminergic medication, long duration of dopaminergic treatment, and a personality profile characterized by impulsiveness (Ceravolo, Frosini, Rossi, & Bonuccelli, 2009; Giladi, Weitzman, Schreiber, Shabtai, & Peretz, 2007; Klos, Bower, Josephs, Matsumoto, & Ahlskog, 2005; Voon, Thomsen, et al., 2007; Weintraub et al., 2010; Weintraub et al., 2006). ICDs manifest as addictive behaviours including pathological gambling,

compulsive shopping, binge eating, and hypersexuality (for a review see Voon et al. 2007). Treatment decisions would be aided by an objective method to predict and classify an individual's risk of developing impulsive side effects.

Impaired impulse control is associated with an increased risk of developing ICDs. Pd patients on dopamine replacement therapies exhibit higher levels of impulsivity (Isaias et al., 2008) and disinhibition (Pontone, Williams, Bassett, & Marsh, 2006) than healthy controls, which are both associated with an increased probability of impulsive disorders. There are several reasons to suspect that a RI paradigm could provide a quantifiable measure of risk for ICD development. For instance, D2 dopamine receptors are specifically implicated in RI (Colzato, van den Wildenberg, & Hommel, 2013; Colzato, van den Wildenberg, Van der Does, & Hommel, 2010; Eagle et al., 2011; Ghahremani et al., 2012; Hamidovic, Dlugos, Skol, Palmer, & de Wit, 2009; Nandam et al., 2013) and are a common target of several routinely prescribed dopamine agonist medications known to cause ICDs. Second, RI is impaired in pathological gamblers and individuals with an ICD manifesting as Tourette syndrome (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006). Poletti et al. (2012) identified that difficulty on executive tasks requiring high levels of impulse control such as a RI task may signal increased risk for the development of ICDs in medicated Pd patients, but this has not yet been tested. As impaired inhibitory control has been specifically implicated in individuals with ICDs, SSRTs produced from a RI task may be the most useful dependent variable to provide a quantifiable measure of risk for ICD development.

Without question, the development of ICDs are associated with dopamine agonist (DA) medication (Dodd et al., 2005; Grosset et al., 2006; Klos et al., 2005; Voon et al., 2006; Weintraub et al., 2006), e.g pramipexole, pergolide and ropinirole (Tyne, Medley, Ghadiali, &

Steiger, 2004). The incidence of ICDs is about 14 – 20 % in patients prescribed DAs (Weintraub, 2009; Weintraub et al., 2010; Weintraub et al., 2006). Although *de novo* Pd patients can also develop ICDs in the absence of dopaminergic medication (Antonini et al., 2011; Avanzi et al., 2006), the risk is no higher than for healthy controls (Weintraub, Papay, & Siderowf, 2013). One idea is that early detection of impaired impulse control may prevent ICDs from developing by informing clinicians and guiding medication selection and timing. Once dopaminergic therapy begins, early detection of impaired impulse control would signal the need for monitoring at-risk patients (Voon, Potenza, & Thomsen, 2007).

It is worth briefly re-examining how dopaminergic medication may trigger ICDs. ICDs are essentially extreme cases of dopaminergic dysregulation of voluntary and goal-directed behaviours. The current hypothesis on the mechanistic root of ICDs is the hyperdopaminergic state of the MCL system in early Pd (Cools, 2006; Sawamoto et al., 2008) which is then exacerbated by dopaminergic medication. Medication is targeted at optimising motor function by augmenting depleted nigrostriatal dopamine. Unfortunately medications lack network specificity, therefore the relatively preserved ventral striatum, caudate nucleus and PFC within cognitive and MCL networks can become hyperdopaminergic (Cools, 2006; Vaillancourt, Schonfeld, Kwak, Bohnen, & Seidler, 2013), deviating from their optimal dopaminergic activity and function along their individual inverted-U curve. Increasing tonic dopamine activity in the PFC and ventral striatum disrupts associative learning and behaviour modification (Goto & Grace, 2005; Schultz, 2002). Contextual behaviour modification is impaired during healthy aging (Chowdhury et al., 2013) and in Pd patients (Rowe et al., 2008). Further disruption of this behavioural mechanism through dopamine dysregulation is hypothesized to contribute to the development of ICDs. Interestingly however, at a group level DA administration does not necessarily impair RI in Pd

(Antonelli et al., 2013). Using the delay discounting task and go/no-go RI task, Antonelli et al. found pramipexole increased impulsivity during the delay discount task but had no effect on reaction time or frequency of unsuccessful no-go trials in the RI task. Treatment with pramipexole influenced cognitive impulse control (impulsive choice), but not motor impulse control (impulsive action). The lack of effect on motor impulse control may be partly due to the go/no-go task design, as discussed in section 3.1. Nevertheless, Wylie et al. (2012) found measures of motor impulse control could not dissociate between Pd patients with and without ICDs.

5.2 Does genetic makeup predispose some individuals to impulse control disorders?

As in many pathological conditions, responses to both disease and treatment options may depend on an individual's genetic profile. Here we briefly review what is known about genes involved in dopaminergic transmission. Dopamine regulating genes are integrally involved in the functioning of BG-thalamocortical networks and are postulated to dictate response to dopaminergic medication. Inter-individual differences in DNA sequences exist as a result of mutations, referred to as polymorphisms. Crucially, genetic variation within the dopaminergic system can influence traits known to be modulated by dopamine, such as impulsivity (Nandam et al., 2013; Nemoda et al., 2011). Genetic variability will have the greatest influence on behaviour when dopamine neurotransmission deviates from close-to-optimal levels i.e. dopamine dysregulation, for example at either extreme end of the inverted-U relationship (Figure 2).

Here we identify five genes that are particularly influential in dopamine neurotransmission, most of which have received some attention related to ICDs. Catechol-O-methyltransferase (COMT) and dopamine transporter (DAT) genes influence synaptic dopamine concentrations.

COMT polymorphisms affect executive function, including impulse control (Blasi et al., 2005; Colzato, Waszak, et al., 2010; Congdon et al., 2009; Diamond et al., 2004; Fallon et al., 2013; Farrell et al., 2012; Foltynie et al., 2004; Hoogland et al., 2010; Krämer et al., 2007; Williams-Gray et al., 2008; Williams-Gray, Hampshire, Robbins, Owen, & Barker, 2007).

Polymorphisms within the genes encoding for the dopamine D1 (DRD1, rs4532), D2 (DRD2, rs1800497) and D3 (DRD3, rs6280) receptors can affect dopamine neurotransmission (Nemoda et al., 2011; Pearson-Fuhrhop, Minton, Acevedo, Shahbaba, & Cramer, 2013). DRD2s are specifically implicated in RI performance (Colzato, van den Wildenberg, et al., 2010; Ghahremani et al., 2012; Hamidovic et al., 2009; Nandam et al., 2013) and their impact is magnified during aging (Colzato et al., 2013). Mutations within DRD1 (Comings et al., 1997) and DRD3 (Lee et al., 2009) have been associated with impulsive behaviours. D3 receptors are abundant in the ventral striatum (Gurevich & Joyce, 1999), which forms part of the MCL network. The link between DRD3 polymorphisms and impulsive behaviour in Pd provides further support for the involvement of the MCL network in ICDs.

The combined effect on dopaminergic neurotransmission of mutations within these five genes has recently been quantified by determining a dopamine gene score for 50 individuals engaged in a motor learning task (Pearson-Fuhrhop et al., 2013). The effect of dopaminergic medication on motor learning varied with dopamine gene score: participants with lower levels of dopamine neurotransmission showed an improvement in motor learning on dopaminergic medication, whereas medication had a detrimental effect on those with higher dopamine gene scores. Dopaminergic genes may also determine how an individual responds to dopaminergic medication in the context of impulse control. Indeed, DAs produce opposite individual effects on impulse control that are dependent on a patient's baseline performance without medication

(Wylie et al., 2012). It is our contention that investigating individual dopamine genetic profiles in combination with cognitive-motor impulse control measures may reveal important information that can account for the divergent DA effects on impulse control and possible susceptibility to ICDs, which in turn could lead to more individualized treatment of Pd. For these reasons, considering only the effect of dopaminergic medication on RI performance, without allowing for dopaminergic gene profiles, may not be capable of identifying risk of ICDs.

6. Conclusion

Motor, cognitive, and limbic systems are impaired in Pd due to dopaminergic dysregulation. RI may offer potential utility and RI tasks may provide salient biomarkers which inform diagnostic criteria as well as identifying individuals at risk of developing ICDs. Given the contextually rich dataset provided by a RI task, the salient measures provided during the pre- and post-diagnostic stage are most likely to be in different behavioural contexts. Execution trials of a RI task, rather than SSRT, might provide the most sensitive and useful biomarkers during the pre-diagnostic period. In contrast, it is more likely that SSRT measures will provide the more useful markers post-diagnosis when evaluating ICD risk. Our contention is that further research is warranted to determine if RI tasks should form part of an objective, combined motor and non-motor test battery, to assist with earlier diagnosis. To inform individualized treatment decisions post-diagnosis, the risk of ICDs may best be determined through assessments and screening that may include RI measures and obtaining a dopaminergic genetic profile.

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Figure Legends:

FIGURE 1. Model of the cortico-BG-thalamocortical sensorimotor networks involved in movement execution and inhibitory control. The ‘direct’,’ indirect’ and ‘hyperdirect’ pathways are represented at a basic level. Grey boxes indicate nuclei of functional BG; arrows indicate facilitatory input; filled circles indicate inhibitory input; open diamond indicates dopamine-dependent input; IFC, inferior frontal cortex; SNpc, substantia nigra pars compacta; GPe, globus pallidus externus; STN, subthalamic nucleus; GPi, globus pallidus internus; SNpr, substantia nigra pars reticulata; pre-SMA, pre-supplementary motor area; M1, primary motor cortex.

FIGURE 2. The task-dependent inverted-U relationship between function and dopaminergic neurotransmission in the PFC. Area on the curve between dashed vertical lines denotes optimal function and transmission of dopamine. Healthy young adults lie to the left of the curve, early Pd patients to the right. Factors which move individuals to the right of the curve include dopaminergic medication and neurophysiological changes in early Pd. As Pd progresses, an individual moves towards the left along the curve. An individual’s position and movement along

the curve will also depend on their dopaminergic genetic profile, and whether it causes higher or lower baseline dopamine neurotransmission. PFC: prefrontal cortex; Pd: Parkinson's disease.

FIGURE 3. Schematics of Go/No-Go (*A*), Stop Signal (*B*) and Anticipatory Response Inhibition (*C*) task displays during execution and inhibition trials. The distribution of Go responses is represented for the Stop Signal and Anticipatory Response Inhibition tasks (*right*), demonstrating how the latency of the inhibition process is calculated (stop signal reaction time) using assumptions of the race model. *p*(respond): probability of a response.

FIGURE 4. Results from an ARI task with individual's with focal hand dystonia (FHD) (*A,B*) and *de novo* Pd patients (*C, D*). The target is presented at 800 ms in both studies. **A:** Patients with FHD require an earlier mean stop time to achieve 50 % successful inhibition (R50) compared to healthy age-matched controls. **B:** At the majority of stop times prior to the target, patients with FHD demonstrate a greater probability of EMG bursts during successfully inhibited responses compared to controls. FHD patients had greater difficulty inhibiting their pre-planned response than controls. (Reproduced with permission from Stinear & Byblow 2004) Error bars denote standard deviation. *p<0.05, **p<0.01. **C**: EMG traces from extensor digitorum communis during an ARI execution trial. Top: Individual trace from a *de novo* Pd patient, motor response at 815 ms. Note the two small bursts of EMG prior to the muscle activity that produced the motor response. Bottom: Individual trace from a healthy age-matched adult, motor response at 792 ms. Note the lack of EMG activity prior to the burst of muscle activity that produced the motor response. (Unpublished data)**. D**: Individual data from 5 *de novo* Pd patients and 5 healthy age-matched adults, showing the probability of these early, ineffective bursts of EMG activity. *De novo* Pd patients are more likely to produce these premature EMG responses. (Unpublished data)**.** EMG: electromyography; Pd: Parkinson's disease.

Table Legends:

TABLE 1: *p*(respond) = 0.5 = 50 % probability of a behavioural response.